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Teneligliptin: Heralding Change in Type 2 Diabetes

Manish Maladkar*, Srividya Sankar, Kushal Kamat

Aristo Pharmaceuticals Pvt. Ltd., Mumbai, India
Email: *scientific@aristopharma.org

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Abstract

"Sweet is Sweet but until it is not too Sweet". As the sweet spoon of diabetes challenges the global population, diabetic organizations across the globe call for unanimous resonance of *Diabetes Voice* to tackle diabetes with healthy living. With the discovery of new pathophysiology associated with diabetes, patients are gaining access to the newer therapeutic classes. Teneligliptin, a third generation DPP-4 inhibitor exhibits unique "J-shaped" structure with "anchor-lock domain" mechanism which provides potent & long duration of action. It acts like an insulin/glucagon modulator controlling blood glucose over 24 hours. It is effective in tackling short-term glycemic fluctuations and improvement in *β*-cell parameters is observed soon after treatment. Half-life of 26.9 hours ensures once a day administration. Because the metabolites of this drug are eliminated via renal and hepatic excretion, no dose adjustment is necessary in patients with renal impairment. Improvement in lipid profile, LV function, adiponectin levels & natriuretic effect is among the added pleiotropic benefits. With the effective glycemic control & capability for improvement in *β*-cell function, Teneligliptin promises to be a preferable antidiabetic agent with long-term efficacy & safety in patients with type 2 diabetes. The objective of this paper is to provide a comprehensive datum analysis of Teneligliptin in the management of type 2 diabetes. It summarizes the unique pharmacodynamic & pharmacokinetic advantages of Teneligliptin and additionally its pleiotropic benefits of cardioprotection. It provides a comprehensive comparison of Teneligliptin vis-à-vis other gliptins in the class & provides a concise summary of all clinical trials till the date with Teneligliptin monotherapy & combination with other antidiabetic drugs.

Keywords

Teneligliptin, DPP-4 Inhibitors, GLP-1, *β*-Cell Preservation, Pleiotropic Benefits, Gliptins

*Corresponding author.

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1. Introduction

Diabetes, in all its forms, imposes unacceptably high human, social & economic costs on countries at all income levels [1]. 415 million people are estimated to have diabetes with dramatic increases seen in countries all over the world. The overwhelming burden of diabetes strikes both low- & middle-income countries, where four out of five people are diagnosed with diabetes. Around 193 million, close to half of the people with diabetes, are unaware of their disease. Inadequate glycemic control results in microvascular & macrovascular complications such as cardiovascular diseases, peripheral arterial disease, retinopathy, nephropathy & neuropathy. From a simple disease of insulin deficiency, to a bifactoral model of insulin deficiency & resistance, to a multifactorial condition, diabetes is a challenging proposition [2]. Over the years as the understanding of diabetes pathophysiology has evolved, there has been a tremendous improvement in the way we approach & manage this disease [3]. The triumvirate of impaired insulin secretion, increased hepatic glucose production & decreased peripheral glucose utilization has always remained the core defects responsible for the development & progression of type 2 diabetes. However, as diabetic research has evolved, the gut (gastrointestinal tissues) has emerged as an add-on affiliate that contributes to pathogenesis of type 2 diabetes. Intestinal secretion of insulin or incretins namely, glucagon-like peptide (GLP-1) & glucose-dependent insulinotropic polypeptide (GIP) governs blood glucose homeostasis. They stimulate insulin biosynthesis & enhance insulin secretion from β-cell of pancreas. GLP-1 and not GIP additionally suppresses glucagon secretion from α-cell of pancreas thereby reducing hepatic glucose output [4]. GLP-1 being α/β cell modulator has evolved as a successful drug target. Following release, incretin hormones are rapidly inactivated by dipeptidyl peptidase-4 (DPP-4) enzyme. This has opened up avenues for treatment strategies targeting intestinal secretion of insulin or incretins. These include incretin mimetics—GLP-1 receptor agonist because they mimic the actions of GLP-1 & incretin enhancers—DPP-4 inhibitors/Gliptins because they inhibit the DPP-4 enzyme that degrades GLP-1 [4]. Apart from being insulin/glucagon modulators, they do not cause hypoglycemia or weight gain, and clinical studies have shown capability for improvement in β-cell function [5]. These classes differentiate themselves from traditional anti-diabetic agents due to their β-cell preservation capabilities which could be linked to slow the progression of type 2 diabetes. GLP-1 agonists, e.g. exenatide are to be administered subcutaneously while DPP-4 inhibitors, e.g. gliptins are administered orally. Additionally, GLP-1 agonists are associated with high incidences of nausea [6]. All these factors make DPP-4 inhibitors potentially the better candidate for combination therapy with other anti-diabetic drugs.

Teneligliptin is a third generation DPP-4 inhibitor approved for treatment of type 2 diabetes. It is currently available in Japan, South Korea, Argentina and India. It is under pre-registration in Indonesia & under Phase I trials in US & Phase II trials in Denmark, Germany, Hungary, Lithuania, Poland, Romania & UK. The aim of this paper is to provide a comprehensive datum analysis of Teneligliptin in the management of type 2 diabetes. This paper summarizes the unique pharmacodynamic & pharmacokinetic advantages of Teneligliptin in addition to its pleiotropic benefits of cardioprotection. It provides a concise summary of all clinical trials till the date with Teneligliptin monotherapy & combination with other antidiabetic drugs.

2. Pharmacodynamic Advantage of Teneligliptin

2.1. Unique Structural Advantage

All DPP-4 inhibitors are similar in terms of mechanism of action & safety, however, they differ considerably in terms of pharmacokinetic & pharmacodynamic profiles. DPP-4 enzyme has several binding sites namely S_1, S_2, S_1', S_2' & S_2 extensive subunit as shown in **Figure 1**. An interaction of DPP-4 inhibitors with S_1 & S_2 is considered to be the fundamental interaction required for DPP-4 interaction. Additional interaction with S_1', S_2' & S_2 extensive site may further increase the DPP-4 inhibition. DPP-4 inhibitors are classified according to their interactions with DPP-4 enzymes. DPP-4 inhibitors are classified as Class 1, Class 2 and Class 3 based on their interaction at DPP-4 subsites. Class 1 inhibitors (Vildagliptin & Saxagliptin) bind to S_1 & S_2 and are considered as fundamental/basic inhibitors. Class 2 (Alogliptin & Linagliptin) bind to additional site of S_1, S_2 & S_1' and may produce more DPP-4 inhibition than Class 1, Linagliptin additionally binds to the S_2' subsite. Class 3 inhibitors (Sitagliptin & Teneligliptin) binds to S_1, S_2 & additional site of S_2 extensive and produce more extensive DPP-4 inhibition [7] (**Table 1**).

Teneligliptin consists of a considerably rigid "J-shaped" structure formed by five rings, four of which are directly connected to DPP-4 which provides strongest binding to DPP-4 enzymes as compared to other gliptins (**Figure 2**).

Figure 1. DPP-4 enzyme with binding sites.

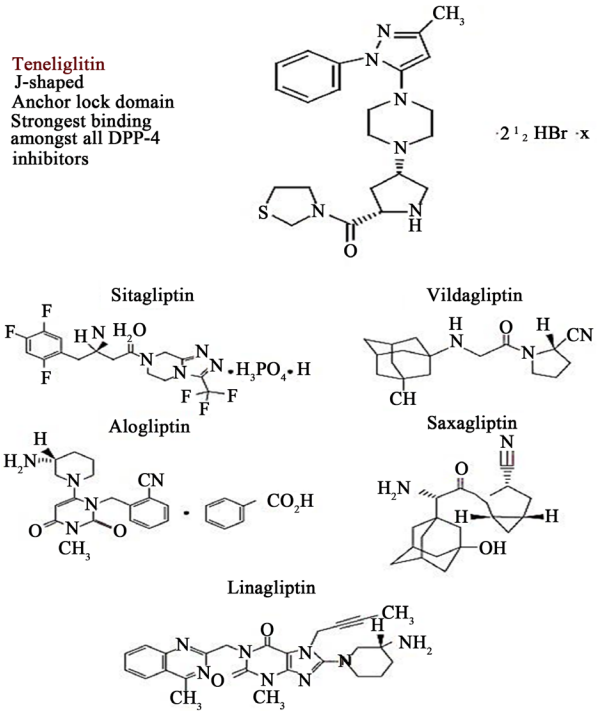
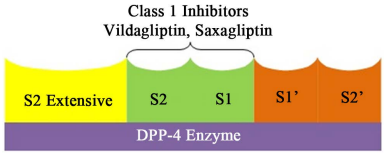
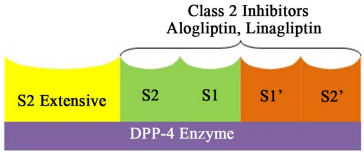
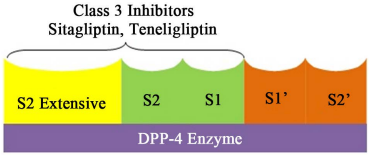


Figure 2. Summary of chemical structure of various gliptins.

Table 1. Summary of the interactions of various DPP-4 inhibitors with DPP-4 enzymes.

Class	DPP-4inhibitors	Binding at DPP-4	Interaction with DPP-4 at various sites	Details
1	Vildagliptin & Saxagliptin	S_1 & S_2 Subsites		• Fundamental/basic interaction required for DPP-4 inhibition • Cyanopyrrolidine moieties bind to S_1 • Hydroxyadamantyl groups bind to S_2 • Saxagliptin has 5-fold higher activity than Vildagliptin
2	Alogliptin & Linagliptin	S_1, S_2, S_1' & S_2' subsites		• Alogliptin binds to S_1, S_2 & S_1' • Linagliptin binds to S_1, S_2, S_1' & S_2' • Linagliptin has 8-fold higher activity than Alogliptin
3	Sitagliptin & Teneligliptin	S_1,S_2 & S_2 extensive subsites		• Teneligliptin has 5 fold higher activity than Sitagliptin due to J-shaped anchor-lock domain, strong covalent bonds with DPP-4 & more extensive S_2 extensive binding than Sitagliptin

For Teneligliptin, introduction of the "anchor lock domain", which binds to the S_2 extensive subsite, increased the activity by 1500-fold over the corresponding fragment that binds to S_1 & S_2 only. Although, Teneligliptin & Sitagliptin both fall in Class 3 & both bind to S_2 extensive subunit, Teneligliptin has 5-fold higher activity than Sitagliptin for DPP-4 enzymes. Teneligliptin has total contact area of 2.08 nm^2 while Sitagliptin has total contact area of 1.90 nm^2. Teneligliptin may bind more tightly to the S_2 extensive subsite as a result of stronger hydrophobic interactions mediated by the "anchor lock domain". Binding of the anchor lock domain may relate to the residence time of DPP-4 inhibition and the long in vivo duration of action [7]. Inhibition of the DPP-4 substrate by Teneligliptin occurs in a manner that involves formation of a reversible covalent enzyme–inhibitor complex. This complex binds and dissociates from the catalytic site of the DPP-4 substrate very slowly resulting in persistent DPP-4 inhibition even after the drug is inactivated. This means that the catalytic activity remains inhibited even after the free drug has been cleared from the circulation. Binding to the S_2 extensive subsite, DPP-4 inhibitors can increase not only their inhibitory activity but also their selectivity towards other DPP enzymes. The J-shape and anchor-lock domain, contributes to the strong inhibitory function and potency of this drug with the lowest IC_{50} value (0.37 nmol/L) as depicted in **Table 2**. It is extremely selective for DPP-4 as compared to DPP-8 (703 fold) & DPP-9 (1460 fold) [8].

2.2. Sustained DPP-4 Inhibition & High GLP-1 Concentration

The plasma concentrations of Teneligliptin after administration of dosages 10 or 20 mg once daily for 4 weeks revealed a median time to maximum concentration (C_{max}) of 1.0 hour with both dosages respectively. The maximum percentage of the inhibition in plasma DPP-4 activity was achieved within 2 hours after administration and was 81.3% and 89.7% with Teneligliptin 10 and 20 mg, respectively [10]. The percentage inhibition of DPP-4 activity at 24 hrs, after administration was 53.1% in Teneligliptin 10 mg group & 61.8% in Teneligliptin 20 mg group. The active plasma GLP-1 concentration was higher after Teneligliptin administration than placebo throughout the day, even at 24 hours after administration. The $AUC_{0\text{-}2h}$ values for the active GLP-1 concentration after breakfast, lunch and dinner were 8.0, 8.4 and 7.8 pmol·h/L respectively, in Teneligliptin 10 mg group and 8.3, 7.9, and 8.6 pmol·h/L respectively, in Teneligliptin 20 mg group [10]. As compared to Teneligliptin 10 mg group, increase in $AUC_{0\text{-}2h}$ for active GLP-1 concentration was slightly greater after dinner in Teneligliptin 20 mg group. Differences in the $AUC_{0\text{-}2h}$ for the active GLP-1 concentration between both the Teneligliptin-treated groups and the placebo group were statistically significant ($p < 0.001$) (**Figure 3**).

2.3. Insulin/Glucagon Modulator

T. Kadowaki *et al.* [11] studied the effects of Teneligliptin on insulin, glucagon, C-peptide & other parameters. $AUC_{0\text{-}2h}$ for postprandial insulin and postprandial C-peptide increased significantly in the Teneligliptin-treated groups compared with the placebo group. There were no significant differences between groups in the $AUC_{0\text{-}2h}$ for postprandial glucagon (data not shown), however, glucagon secretion tended to be lower in the Teneligliptin-treated groups (**Figure 4**).

2.4. 24 Hours Glucose Control

T. Eto *et al.* [12] reported effects of Teneligliptin 10 mg & 20 mg on fasting plasma glucose (FPG) & 2-hour

Table 2. Summary of IC_{50} values of various gliptins [9].

DPP-4 Inhibitor	IC_{50} Values (nmol/L)
Sitagliptin	19
Vildagliptin	62
Saxagliptin	50
Linagliptin	1
Alogliptin	24
Teneligliptin	0.37

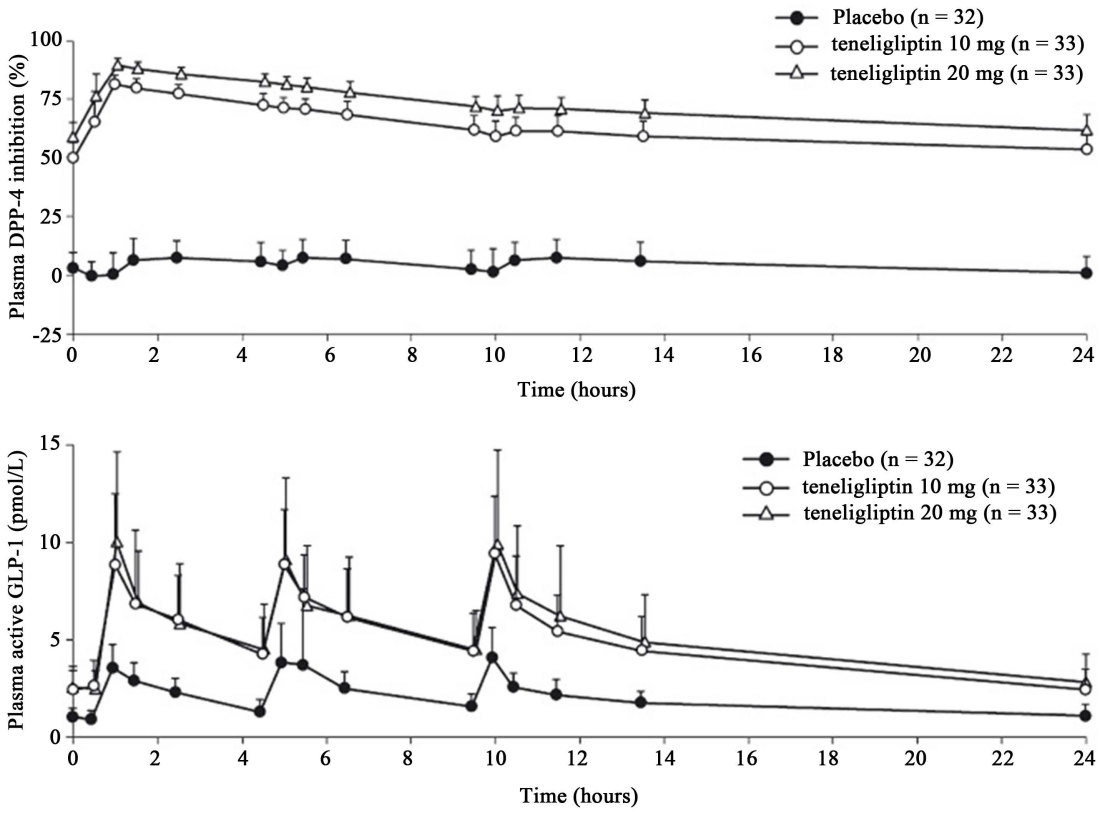


Figure 3. The percentage inhibition of plasma DPP-4 activity and plasma active GLP-1 concentrations in Teneligliptin 10 mg & 20 mg groups as compared to placebo are shown. Data for Teneligliptin 10 mg is represented in open circles, Teneligliptin 20 mg in open triangles and placebo in closed circles. Values are mean + SD. Differences between Teneligliptin 10 mg & 20 mg group were not tested statistically. Study reports one patient in Teneligliptin 10 mg group did not take the study drug on the penultimate day of the 4-week treatment phase; therefore, all pharmacokinetic and pharmacodynamic data from this patient were excluded from the analysis.

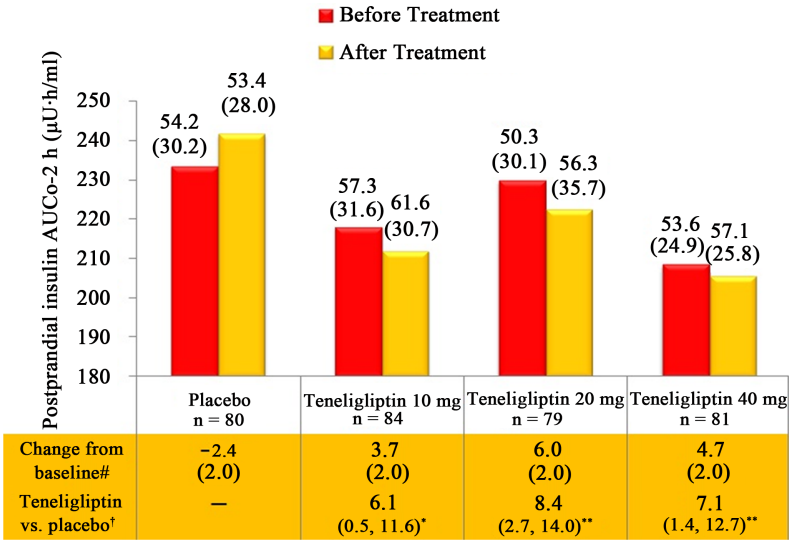


Figure 4. Postprandial insulin $AUC_{0\text{-}2h}$ after administration of Teneligliptin 10mg, 20 mg, 40 mg vs placebo. $AUC_{0\text{-}2h}$ area under the curve from 0 to 2 h after standard meal. ANCOVA was performed using treatment group as the fixed factor and baseline value as a covariate. $^{*}p < 0.05$; $^{**}p < 0.01$ vs placebo. $^{\#}$values are means (s.d.), except least-squares means (s.e.). †values are means (s.d.), except least-squares means (95% confidence intervals).

postprandial glucose (PPG) after each meal. Both Teneligliptin-treated groups showed significantly smaller 2-h PPG, 24-h mean glucose and FPG values than the placebo group. The differences between Teneligliptin 10 mg group & placebo in changes in 2-h PPG after each meal were −50.7 ± 7.8, −34.8 ± 9.2 and −37.5 ± 7.5 mg/dl [least squares (LS) means ± standard error (s.e.), all, $p < 0.001$] at breakfast, lunch and dinner, respectively. The corresponding LS means ± s.e. for Teneligliptin 20 mg versus placebo were −38.1 ± 7.8, −28.6 ± 9.2 and −36.1 ± 7.5 mg/dl, respectively ($p < 0.001$, $p < 0.01$, $p < 0.001$, respectively). Both doses of Teneligliptin increased postprandial plasma active glucagon-like peptide-1 concentrations compared with placebo. The incidences of adverse events and drug-related adverse events were similar among both groups. There were no hypoglycaemic symptoms or serious adverse events.

2.5. *β*-Cell Preservation

DPP-4 inhibitors were reported to promote *β*-cell proliferation, in addition to their *β*-cell protective effects (achieved by inhibiting their apoptosis), resulting in functional improvements. Glycemic effect of Teneligliptin is obtained through activating *β*-cell function as well as decreasing insulin resistance. Teneligliptin has shown improvements in markers of *β*-cell function including homeostatic model assessment of *β*-cell function (HOMA-*β*), Insulinogenic Index (IGI; an estimate of early insulin secretion), Secretory units of islets in transplantation (SUIT) index, homeostatic model assessment for insulin resistance (HOMA-R). Rika Ito *et al.* [13] studied changes in insulin secretion before & after Teneligliptin treatment for 12 weeks in 30 diabetic patients. parameters like HbA1c, IGI, HOMA-*β*, HOMA-R, SUIT index were measured. IGI was calculated by dividing the increment in insulin during the first 30 min by the increment in glucose over the same period [(30 min insulin-0 min insulin)/(30 min glucose-0 min glucose) = IGI30 min]. The SUIT index was calculated at 0, 30, 60, 90, and 120 min during the oral glucose tolerance tests (OGTT) (SUIT index0, SUIT index 30, SUIT index 60, SUIT index 90, and SUIT index120, respectively) using the following formula: C-peptide immunoreactivity (CPR) (ng/mL) × 1500/[PG (mg/dL)-61.7]. HOMA-*β* was calculated using formula: fasting insulin (μU/mL) × 360/[fasting PG (mg/dl) - 63], HOMA-R was calculated using formula: fasting PG (mg/dL) × fasting insulin (μU/mL)/405. HbA1c significantly decreased from 8.3 ± 0.4% at baseline to 6.3% ± 0.2% after 12 weeks of Teneligliptin treatment ($p < 0.05$). *β*-cell function assessed by $IGI_{30min,}$ AUC_{120min} insulin, and the AUC_{120min} SUIT index significantly increased (0.16 ± 0.05 vs. 0.28 ± 0.06; $p < 0.05$, 2692 ± 333 μU·2 h/mL vs 3537 ± 361 μU·2 h/mL; $p < 0.01$ and 4261 ± 442 vs 8290 ± 1147; $p < 0.01$). HOMA-R decreased (2.52 ± 0.40 vs 1.71 ± 0.26; $p < 0.05$; values are mean ± standard error). Eiji Kutoh *et al.* [14] studied the effect of Teneligliptin 20 mg/day as an initial therapy in 31 newly diagnosed type 2 diabetes patients mean age 58.29 ± 14.95 for 3 months. Significant reductions in HbA1c (from 10.34 ± 2.06 to 8.38 ± 2.23%; $p < 0.00001$) and fasting blood glucose (from 211.3 ± 68.4 to 167.3 ± 70.2 mg/dL; $p < 0.0002$) levels were observed without any clinically significant adverse events. Homeostasis model assessment *β*-cell function (HOMA-*β*) significantly increased (from 24.04 ± 31.14 to 40.23 ± 40.98; $p < 0.00001$), while Homeostasis model assessment-insulin resistance (HOMA-R) decreased (from 3.74 ± 4.28 to 2.90 ± 2.16; p-n.s.) after treatment with Teneligliptin. The improvement in *β*-cell markers were reported in several studies after treatment with Teneligliptin.

2.6. Reduction in Short-Term Glycemic Fluctuations

Glycemic variability (GV) refers to swings in blood glucose levels (FPG & PPG) that occurs throughout the day. GV considers the intraday glycemic excursions, including episodes of hyperglycemia and hypoglycemia as well as blood glucose fluctuations that occur at the same time on different days [15]. Despite the same HbA1c levels at 3 months, patients tend to have marked glycemic variability throughout the day which is directly linked to microvascular & macrovascular complications. Glycemic variability can be assessed through various parameters: mean amplitude of glycemic excursions (MAGE), glycated albumin (GA) & 1,5-anhydroglucitol (1,5-AG) which may have clinical utility for diagnosing and evaluating glycemic variability and predicting diabetic complications. Mean amplitude of glycemic excursion (MAGE) computes the average height of glucose excursions that exceed the standard deviation for a given day. It includes only peak-to-nadir or nadir-to-peak excursions in its calculation, depending on which type of excursion occurs first in the day's data. [16] GA is a better marker than HbA1c for short term variations of glycemic control. HbA1c predicts glycemia over 2-3 months; GA predicts glycemia over 2 - 3 weeks [17]. High GA increases risk of atherosclerosis [18]. 1, 5-AG is also a good

marker of short term episodes of hyperglycemia such as PPG & other short term glucose excursions. 1, 5 AG predicts glycemia over 1 - 3 days (mild to moderate hyperglycemia) [19]. Low 1,5-AG increases risk of atherosclerosis [20]. In addition to HbA1c, FPG & PPG are important indicators for the treatment of T2DM. Acute blood glucose fluctuations lead to oxidative stress, inflammation & endothelial dysfunction [21] [22]. Daily glucose fluctuations exhibit more specific triggering effect on oxidative stress than chronic hyperglycemia [23]. With changes in our dietary lifestyle and irregular eating habits which affect daily glucose fluctuations, it is important to normalize daily blood glucose fluctuations by suppressing post prandial hyperglycemia at all three meals daily. It is therefore important to note that maintaining sustained glycemic control (not only HbA1c, but also FPG & PPG-Glycemic Variability) is required to reduce the risk of diabetic complications [24]. Seiichi Tanaka *et al.* [25] studied the effect of Teneligliptin 20 mg once daily for ameliorating glucose fluctuations in 26 type 2 diabetic patients receiving insulin therapy, with or without other antidiabetes drugs, and using continuous glucose monitoring (CGM). Variations in 24-hr. blood glucose levels measured by CGM during add-on treatment with Teneligliptin 20 mg are shown in **Figure 5**. Add-on treatment with Teneligliptin 20 mg significantly decreased both fasting and postprandial glucose levels on Days 5 - 7. Add-on treatment with Teneligliptin led to significant decrease in 24-hour mean glucose levels ($p < 0.001$) and improvement in parameters of short term glycemic fluctuations over 3 days like decrease in MAGE (before treatment: 90.1 ± 46.7 mg/dL to after treatment: 85.5 ± 34.3 mg/dL; $p < 0.05$), decrease in GA (before treatment: −1.10% ± 1.13% to after treatment: −1.64% ± 1.41%; $p < 0.05$) & increase in 1,5-AG (before treatment: 0.40 ± 0.34 to after treatment: 0.97 ± 0.67; $p < 0.05$). Improvement in GA & 1,5-AG is seen in several studies over 3-6 months after add-on Teneligliptin treatment (**Figure 6**).

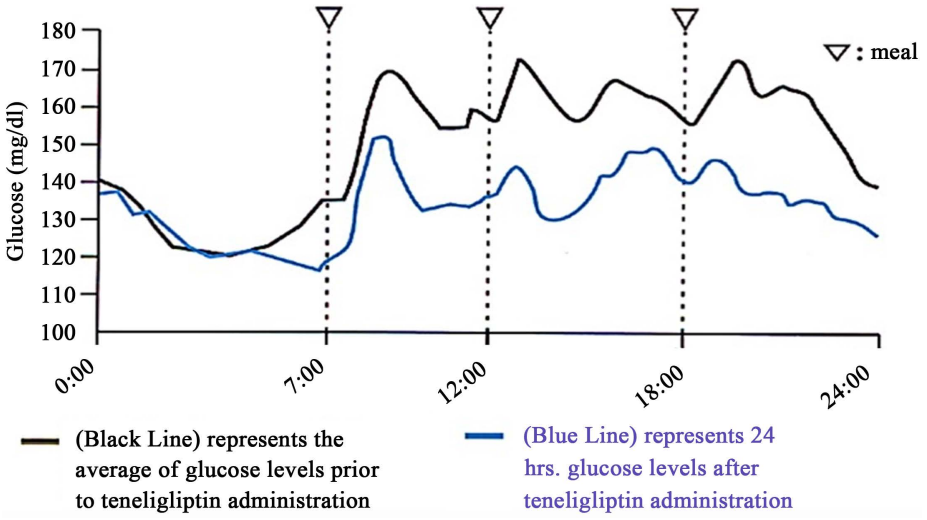


Figure 5. The 24-h glucose profiles before and after administration of Teneligliptin in patients with placebo type 2 diabetes receiving insulin therapy, with or without other antidiabetes drugs [25].

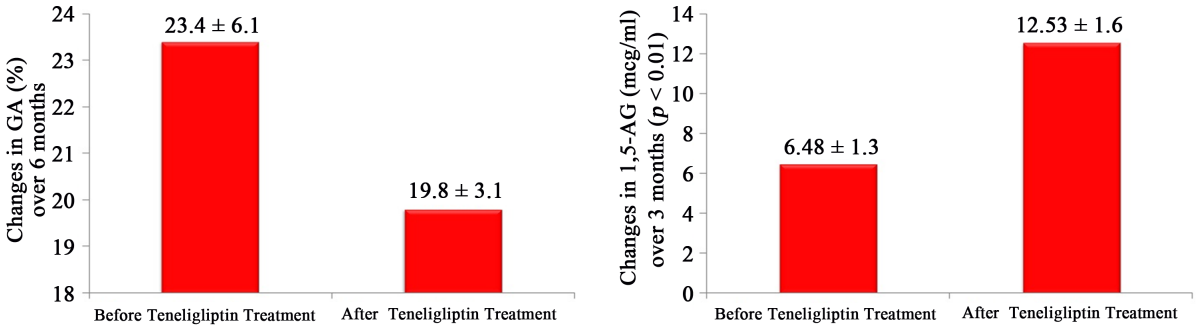


Figure 6. Mean changes with administration of Teneligliptin in indexes of blood glucose control- glycated albumin (GA) [25] & 1,5-anhydro-d-glucitol (1,5-AG): n = 11, $p < 0.01$ [13].

3. Pharmacokinetic Advantage of Teneligliptin

Teneligliptin is rapidly absorbed in healthy volunteers after a single radiolabeled 20 mg dose, with maximum plasma concentrations attained in 1.33 hr [26]. The drug is 78% - 80% bound to plasma proteins [27]. An overview of Teneligliptin pharmacokinetics is mentioned in **Table 3**.

In humans, Teneligliptin is primarily metabolized by cytochrome P450 (CYP) 3A4 & flavin monooxygenases (FMO) 1 and 3 to several metabolites of unknown biological activity [26] [27]. *In vitro*, Teneligliptin is a weak inhibitor of CYP2D6, CYP3A4 and FMO, but shows no inhibitory effect on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19 and CYP2E1 [10] [26]. Teneligliptin does not induce CYP3A4 or CYP1A2 [10] [26]. There were no clinically relevant drug-drug interactions when Teneligliptin was co-administered with Ketoconazole (a potent CYP3A4 and P-glycoprotein inhibitor) [28], Metformin [29] or Canagliflozin [30] in healthy volunteers. No clinically relevant effects on the pharmacokinetics of Teneligliptin were observed when it was coadministered with Glimepiride or Pioglitazone [26]. Teneligliptin follows dual mode of excretion *i.e.* renal & hepatic. At least 90% of the radiolabeled dose of Teneligliptin was excreted within 216 h, with 45.4% excreted in the urine and 46.5% excreted in the faeces [29]. Approximately 21% of Teneligliptin is excreted in the urine as unchanged drug [26]. Teneligliptin has long half-life of 26.9 hours which offers convenient once a day administration [27] (**Table 4**).

4. Pleiotropic Benefits of Teneligliptin

4.1. Improvement in Endothelial Function

Daily blood glucose fluctuations have been shown to cause oxidative stress and induce inflammatory markers leading to endothelial dysfunction and arteriosclerosis. There is also evidence that the postprandial glycemic state contributes to atherosclerotic risk [31]. Teneligliptin appears to have potent, sustained effects on glycemic control, which are beneficial in ameliorating the effects of hypoglycemia and postprandial hyperglycemia on the development of diabetes complications [32]. Takehiro Hashikata *et al*. [33] evaluated the effects of Teneligliptin on left ventricular function in 29 type 2 diabetic patients for 3 months. Improvement was seen not only in LV function (LV ejection fraction, 62.0% ± 6.5% to 64.5% ± 5.0%; $p = 0.01$; peak early diastolic velocity/basal septal diastolic velocity (E/e) ratio, 13.3 ± 4.1 to 11.9 ± 3.3; $p = 0.01$) but also in endothelial function (reactive hyperemia peripheral arterial tonometry [RHPAT] index; 1.58 ± 0.47 to 2.01 ± 0.72; $p < 0.01$). Adiponectin is an adipocyte-derived hormone that plays an important role in the regulation of insulin sensitivity & energy homeostasis. In metabolic disorder like obesity, there is decrease in adiponectin levels in adipocytes. Adiponectin receptor is involved in regulating glucose uptake promotion & fatty acid oxidation. Enhanced adiponectin levels, in turn, increases protection against inflammation, insulin resistance & cardiovascular disorders. Circulating adiponectin levels increased (27.0 ± 38.5 pg/mL to 42.7 ± 33.2 pg/mL; $p < 0.01$) without changes in patient body weight after treatment with Teneligliptin.

4.2. Improvement in Lipid Profile

M. Kusunoki *et al.* [34] have shown beneficial effect of Teneligliptin on lipid profile. 14-week treatment with Teneligliptin 20 mg/day showed significant improvement in lipid profiles along with improvement in blood glucose & HbA1c (**Table 5**).

Table 3. Abridged pharmacokinetics of Teneligliptin.

Parameters	
Absorption	Oral Cmax 180.20 ng/mL Tmax 1.8 hrs for 20 mg Not affected by food
Protein binding	78% - 80%
Metabolism	CYP450 3A4 & FMO 1 - 3
Excretion	45.4% excreted in the urine & 46.5% excreted in the faces
$T_{1/2}$	26.9 hrs

Table 4. Comparison of pharmacokinetic profile of Teneligliptin with various gliptins.

	Teneligliptin	Sitagliptin	Vildagliptin	Saxagliptin	Alogliptin	Linagliptin
			Absorption			
Route	Oral	Oral	Oral	Oral	Oral	Oral
Bioavailability	63% - 85%	87%	85%	67%	100%	30%
Tmax	1.33 h	1 to 4 h	1.75 h	2 h	1 - 2 h	1.5 h
Effect of food	No	No	No	No	No	No
			Distribution			
Protein Binding	78% - 80%	38%	9.3%	Negligible	20%	70% - 80%
			Metabolism			
CYP	CYP3A4 & FMO 1 & 3	Minor CYP3A4, CYP2C8	Minor (~57% of administered drug catabolized by non-CYP-mediated hydrolysis to an inactive metabolite, LAY151)	CYP P450 3A4/5	Minor CYP2D6, CYP3A4	Not metabolized by CYP
Metabolites	Inactive	Inactive	Inactive	Active (BMS-510849)	Inactive	Inactive
			Excretion			
$T_{1/2}$ (hours [hr])	26.9 hr	2 - 3 hr	3 hr	2.5 hr Metabolite 3.1 hr	21 hr	>100 hr
Clearance (%)	Feces (46.5%) Urine (45.4%)	Feces (13%) Urine (87%)	Feces (15%) Urine (85%)	Feces (22%) Urine (78%)	Feces (13%) Urine (76%)	Feces (85%) Urine (5%)
Drug-Drug interactions	No major clinically relevant drug-drug interactions	Plasma AUC of digoxin was increased by 11%, otherwise no major interaction reported	Low potential for drug interaction	Caution–with drugs metabolized by CYP3A4/5 system (Atazanavir, Clarithromycin, Indinavir, Itraconazole, Ketoconazole, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin)	No significant drug-drug interactions	Rifampin

Table 5. Effects of 14-week 20 mg/day administration of Teneligliptin on serum lipids in Japanese patients with type 2 diabetes.

Lipid parameters	Before	After 14 week administration	*P* value
Total Cholesterol (mg/dl)	196 ± 43	174 ± 29	0.105
HDL−Cholesterol (mg/dl)	55 ± 15	62 ± 16	0.032
LDL−Cholesterol (mg/dl)	122 ± 43	103 ± 29	0.164
Triglyceride (mg/dl)	189 ± 140	114 ± 44	0.080

Data are expressed as mean ± SD (n = 9). Significantly different from the values in the respective before values.

4.3. Natriuretic & Diuretic Effects of Teneligliptin

GLP-1R & DPP-4 are expressed in the renal proximal tubular brush border, where they regulate Na^+ reabsorption [35]. DPP-4 exist in physical complexes with Na^+-H^+ exchanger isoform NHE3 in the brush border membranes of renal proximal tubule cells. The NHE3-DPP-4 complex exists predominantly in the microvilli of renal tubules [36]. DPP-4 inhibition reduces NHE3 activity and consequently induces natriuresis [37]. In addition to this, GLP-1 activation induces diuresis. DPP-4 inhibitors are antidiabetic agents that have diuretic & natriuretic effects, which might contribute in reducing blood pressure. A major proportion of diabetic patients are often di-

agnosed with hypertension. Furthermore, DPP-4 inhibitors have recently been shown to enhance nitric oxide release in hypertensive or diabetic models [38]-[40]. Thus, the action of DPP-4 inhibitors might be favorable for diabetic patients with hypertension. DPP-4 converts intact B-type natriuretic peptide [BNP (1 - 32)] into its des-SerPro form [BNP (3 - 32)] [41]. Diuretic & natriuretic effects of BNP (3 - 32) are less than those of BNP (1 - 32). The relative increase of BNP (1 - 32) because of DPP-4 inhibitors might therefore be effective on diuresis & natriuresis. Masao Moroi *et al.* [42] investigated diuretic & natriuretic effects of Teneliglitpin & whether these were associated with the stimulation of GLP-1R in rats. The study concluded that Teneligliptin (10 mg/kg) had diuretic and natriuretic effects with a reduction of plasma DPP-4 activity over 6 hours. The natriuretic effect of Teneligliptin was inhibited by the GLP-1R antagonist, exendin 9 - 39, whereas the diuresis was not affected. These results suggest that the mechanism of natriuresis was different from that of diuresis, and the natriuresis is associated with the stimulation of GLP-1R.

4.4. Weight Neutral

DPP-4 inhibitors are generally considered to be weight neutral [43]-[45]. In a Phase III trial, 20 mg of Teneligliptin was administered to 151 patients with type 2 diabetes, who were previously treated with diet control and exercise treatment alone. The dose of Teneligliptin was increased to 40 mg in patients with HbA1c levels greater than 7.3% at any time after week 24. The mean body weight change of the patients at week 52 (mean ± SD) was +0.18 ± 2.14 kg ($p = 0.3254$), which indicated that the effect of Teneligliptin on body weight was neutral [10].

5. Clinical Journey of Teneligliptin

The efficacy of Teneligliptin has been evaluated both as monotherapy and combination with other antihyperglycemic agents in patients with type 2 diabetes. Studies evaluating the efficacy of Teneligliptin in patients with Type 2 diabetes and end-stage renal disease (ESRD) who were on haemodialysis are reported. **Table 6** summarizes efficacy of Teneligliptin as monotherapy or as an add-on in adults with type 2 diabetes in various clinical trials. In combination trials with Glimepiride & Pioglitazone, patients from 12 weeks double blind study were switched to 40 weeks open label study. In respective studies, patients were switched from add-on placebo to add-on Teneligliptin (P/T group) or had received add-on Teneligliptin (T/T group) throughout 52 weeks (12 weeks double blind + 40 weeks open label extension) study. Teneligliptin in combination with Glimepiride showed significant improvement in glycaemic control at 12 weeks compared with add-on placebo, in terms of mean changes in HbA1c, FPG and 2-h PPG. At 12 weeks, add-on Teneligliptin also improved several other parameters significantly ($p < 0.01$) including changes in PPG AUC_2, the proinsulin/insulin ratio, HOMA-β. and postprandial glucagon AUC_2. There were no significant between-group differences (BGDs) for changes from baseline in HOMA-R, fasting insulin, fasting glucagon or postprandial insulin AUC_2 [47]. Teneligliptin in combination with Pioglitazone significantly ($p < 0.001$) improved glycaemic control compared with placebo plus Pioglitazone. Several other parameters including changes in PPG AUC_2, the proinsulin/insulin ratio, HOMA-β and postprandial glucagon AUC_2 were also improved significantly ($p < 0.001$) [48]. There were no significant BGDs for changes from baseline in HOMA-R, fasting insulin, fasting glucagon or postprandial insulin AUC_2 There were minimal changes from baseline in bodyweight at 52 weeks in the P/T and T/T groups (0.7 and 0.5 kg; 1.2 and 1.5 kg) [47] [48].

Wakaba Tsuchimochi *et al.* [50] showed that once daily Teneligliptin administration for 3 days significantly lowered postprandial and fasting glucose levels. Significant elevations of fasting and postprandial active GLP-1 and postprandial active GIP levels were observed. Teneligliptin lowered postprandial glucose elevations; 24 h mean blood glucose levels (from 162.6 ± 16.7 to 144.7 ± 13.9 mg/dL; $p = 0.014$), standard deviation of 24 h glucose levels (from 38.9 ± 12.1 to 27.6 ± 12.8 mg/dL; $p = 0.0078$) and mean amplitude of glycemic excursions (MAGE) without hypoglycemia (from 83.1 ± 31.5 to 64.5 ± 29.1 mg/dL; $p = 0.047$). In the same study, a significant elevation was observed in early-phase insulin secretion estimated by Insulinogenic index (before treatment: 0.17 ± 0.06 to after 3 days treatment: 0.29±0.15; $p = 0.002$; values are means ± SD) and oral disposition index (before treatment: 0.031 ± 0.008 to after 3 days treatment: 0.076 ± 0.04; $p = 0.002$; values are means ± SD), and a significant ($p = 0.02$) reduction in postprandial glucagon AUC were observed with Teneligliptin treatment. Oral disposition index was calculated using formula: oral disposition index = Δ immunoreactive insulin (IRI) 0, 30 ($\mu U \cdot mL^{-1}$)/Δ glucose 0, 30 ($mg \cdot dL^{-1}$) × 1/fasting insulin ($\mu U \cdot mL^{-1}$). Improvement in glycemic parameters with add-on Teneligliptin to insulin therapy is shown in several other studies (**Table 7**).

Table 6. Efficacy of once-daily Teneligliptin monotherapy and add-on therapy to glimepiride, pioglitazone & metformin in adults with type 2 diabetes.

Study Design	Regimen (mg)	Study duration (weeks)	No. of patients	Placebo-subtracted LSM change from BL to study end (mean BL value)			HOMA-β	HOMA-R	% Patients with HbA1c < 7.3%	% Patients with HbA1c < 6.8%
				HbA1c (%)	FPG (mg/dL)	2h-PPG (mg/dL)				
Monotherapy [12]	Tene 10 mg	4	33	-	−13.8[*a] (169.2)	Breakfast-50.7[*a] (272.6) Lunch-34.8[*a] (248.9) Dinner-37.5[*a] (255.1)	-	-	-	-
	Tene 20 mg		34		−13.6[*a] (163.1)	Breakfast-38.1[*a] (261.5) Lunch-28.6[***a] (244.5) Dinner-36.1[*a] (245.9)				
	PL		32		(153.6)					
Monotherapy [11]	Tene 10 mg	12	84	−0.9[*] (7.9)	−17.8[*] (148.0)	−50.6[*] (240.0)	4.4[**] (26.0)	0.0 (2.2)	43.8[*b]	30.0[*b]
	Tene 20 mg		79	−0.9[*] (7.8)	−16.9[*] (143.0)	−56.8[*] (231.9)	8.3[*] (23.3)	0.1 (1.8)	53.5[*b]	37.9[*b]
	Tene 40 mg		81	−1.0[*] (7.7)	−20.0[*] (141.9)	−58.6[*] (224.2)	3.6 (26.6)	−0.3 (2.0)	67.0[b]	48.7[*b]
	PL		80	(8.0)	(150.0)	(242.0)	(24.4)	(2.1)		
Monotherapy [46]	Tene 20 mg	24	99	−0.94[$] (7.63)	−21.78[$f] (155.16)	-	12.23[+] (36.24)	−0.24[++] (3.58)	69.39[*g]	34.69[h]
	PL		43	(7.77)	(161.28)	-	(30.91)	(3.25)	20.93[g]	4.65
Add-on Therapy (Tene + Glim) Double-blind [47]	Tene 20 mg + Glim 1 - 4 mg/day	12	96	−1.0[*] (8.4)	−27.1[*] (165.1)	−49.1[*] (258.6)	9.1[*] (25.3)	−0.2 (2.8)	31.6	8.3
	PL+ Glim 1 - 4 mg/day		98	(8.4)	(163.4)	(256.1)	(24.9)	(2.9)	2.1	0.0
Add-on Therapy (Tene + Glim) open label extension study[d] [47]	T/T	40	95	−0.6[*ce]	−7.7[**ce]	−32.8[*ce] (258.6)	9.3[*ce] (25.3)	0.2[c] (2.8)		
	P/T		95	−0.9[*ce]	−14.4[*ce]	−35.6[*ce] (262.8)	8.8[*ce] (24.8)	0.1[c] (3.2)	-	-
Add-on Therapy (Tene + Pio) Double-blind [48]	Tene 20 mg + Pio 15 - 30 mg/day	12	103	−0.7[*] (8.1)	−16.4[*] (150.7)	−51.3[*] (230.9)	6.9[*] (29.8)	−0.6 (2.5)	-	-
	PL+ Pio 15 - 30 mg/day		101	7.9	(145.7)	(221.5)	(25.9)	(2.0)		
Add-on Therapy (Tene + Pio) open label extension study[d] [48]	T/T	40	98	−0.9[*c]	−12.1[*c]	−37.4[*c]	8.1[*c]	0.1[c]	-	-
	P/T		98	−0.7[*c]	−9.1[*c]	−41[*c]	6.4[*c]	0.0[c]		

Continued

Add-on Therapy (Tene + Met) Double-blind [49]	Tene 20 mg + Met ≥1000 mg/day	16	136	−0.9[$] (7.79)	−22.3 [fs] (151.02)[f]	-	12.76 (35.68)	−0.29 (3.10)	64.71[*g]	-
	PL+ Met ≥1000 mg/day		68	(7.72)	(151.02)[f]		(33.39)	(2.87)	13.24[g]	

BL: baseline; HbA1c: glycated haemoglobin; FPG: fasting plasma glucose; PPG: postprandial plasma glucose; LSM: least-square mean; Gli: Glimepiride; Pio: Pioglitazone; Met: Metformin; PL: placebo; Tene: Teneligliptin; HOMA-*β*: Homeostasis model of assessment for beta-cell function; HOMA-R: Homeostasis model of assessment for insulin resistance. [a]Least squares (LS) means vs placebo; [b]Teneligliptin vs Placebo between-group difference; [c] Change from baseline to week 52, mean ± SD (95% CI). [d]Patients from 12 weeks double blind study were switched to 40 weeks open label study. In respective studies, patients were switched from add-on placebo to add-on Teneligliptin (P/T group) or had received add-on Teneligliptin (T/T group) throughout 52 weeks (12 weeks double blind + 40 weeks open label extension) study. [e]p-values are versus vs baseline (Week 12 for the P/T group and Week 0 for the T/T group). [f]Values converted from mmol/L to mg/dL using a conversion factor of 0.05551. [g]Patients achieving a target HbA1c of 7.0%. [h]Patients achieving a target HbA1c of <6.5%. [*]$p < 0.001$ [**]$p < 0.05$[***] $p < 0.01$ [$]$p < 0.0001$ [+]0.0003 [++]0.3611 vs. placebo.

Table 7. Efficacy of once-daily Teneligliptin as an add-on to insulin in type 2 diabetic patients.

Study Design	Regimen	Study duration (Days)	No. of patients		Before treatment	After treatment
Add-on Therapy (Tene + Insulin) [25]	Tene 20 mg + Daily insulin dose of ≤60 units	7	26	Mean glucose level (mg/dL)	148.8 ± 25.7	131.3 ± 17.0[b]
				0:00 - 7:00 h	126.0 ± 7.5	119.0 ± 4.2[b]
				7:00 - 24:00 h	159.1 ± 9.8	138.0 ± 9.1[b]
				SD over 24 h (mg/dL)	32.0 ± 16.2	26.9 ± 10.9[b]
				MAGE (mg/dL)	90.1 ± 46.7	85.5 ± 34.3[a]
				Proportion (%) of time in Hypoglycemia (<70 mg/dL)	1.0 ± 2.4	1.6 ± 2.6
				Hyperglycemia (>140 mg/dL)	59.8 ± 24.7	37.6 ± 22.4[b]

Tene Teneligliptin MAGE mean amplitude of glycemic excursion SD standard deviation—Data are mean SD values. [a]$p < 0.05$, [b]$p < 0.001$ versus before Teneligliptin administration.

Chronic kidney disease is a common complication of type 2 diabetes mellitus. Medical therapy for diabetic patients on dialysis is restricted due to possible renal failure. HbA1c in End Stage Renal Disease (ESRD) patients is not a suitable index for glycemic control. Thus, it has often been difficult to control hyperglycemia in diabetic ESRD patients. Significant decrease in HbA1c & glucose levels was observed in hemodialysis patients after Teneligliptin treatment. Otsuki H *et al.* [51] studied effect of Teneligliptin on 14 hemodialysis patients. 7 (Newly started), 4 (switched from Voglibose 0.2 mg TID) and 3 (switched from Vildagliptin 50 mg OD) patients were treated with Teneligliptin 20 mg OD for a duration of 28 weeks. Significant decrease in HbA1c & glucose levels was observed in hemodialysis patients after Teneligliptin treatment. C-peptide is used for determining insulin secretion in healthy person. However, since the kidney is the major site for C-peptide catabolism & excretion, ESRD patients have elevated C-peptide levels. Significant decrease in GA & increase in C-peptide were observed in hemodialysis patients after Teneligliptin treatment. The study concluded that Teneligliptin 20 mg OD was considered to be more potent than voglibose 0.2 mg TID or vildagliptin 50 mg qd.

In post-hoc analysis of two 52-weeks trials, Teneligliptin monotherapy (n = 363) or add-on therapy to a sulfonylurea, glinide, biguanide or *α*-glucosidase inhibitor (n = 339) significantly reduced mean HbA1c levels at 52 weeks compared with baseline in the overall population (by 0.72%; $p < 0.001$) as shown in **Table 8**. Mean changes from baseline to 52 weeks in bodyweight were minimal including the Teneligliptin monotherapy group (+0.3 kg; $p < 0.01$), Teneligliptin plus Glinide group (+0.5 kg; $p < 0.05$) & Teneligliptin plus Sulfonylurea group (+0.5 kg; $p < 0.01$) [52].

6. Safety of Teneligliptin

In Teneligliptin monotherapy study involving 99 patients [12], adverse events occurring in 28.1% (9/32), 23.5% (8/34) and 18.2% (6/33) of patients in the placebo, and Teneligliptin 10 and 20 mg groups, respectively. The incidence of adverse events was not significantly different between the Teneligliptin and placebo groups. None of

Table 8. Additional HbA1c change of add-on Teneligliptin with other anti-diabetic drugs.

Lipid Parameters	Teneligliptin + Sulphonylurea (n = 89)	Teneligliptin + Glinides (n = 80)	Teneligliptin + Biguanides (n = 95)	Teneligliptin + α-glucosidase inhibitor (n = 75)
Additional HbA1c Change	−0.81	−0.76	−0.76	−0.89

$p < 0.001$.

the patients in any group experienced hypoglycaemic symptoms or serious adverse events. There were no clinically significant abnormal changes in vital signs, electrocardiograms (ECGs) or laboratory measurements, nor were there any notable differences between the treatment groups. In another study involving 324 patients [11], the incidence rates of adverse events were not significantly different among the four treatment groups (placebo, Teneligliptin 10 mg, 20 mg or 40 mg). Nasopharyngitis, ketonuria, glucosuria and proteinuria were reported in ≥5% of patients in any group. Overall, two patients in Teneligliptin 10 mg group, none in Teneligliptin 20 mg, one patient in Teneligliptin 40 mg group and two patients in the placebo group discontinued because of an Adverse Events (AEs). The incidences of Adverse Drug Reactions (ADRs) were not significantly different among the four groups, although the rate tended to be higher in the Teneligliptin 40 mg group compared with the Teneligliptin 10 and 20 mg groups. All ADRs were categorized as mild in intensity. The incidence rates of hypoglycaemia were not significantly different among the four groups. Five episodes of hypoglycaemic symptoms (two in the placebo group and three in the Teneligliptin 40 mg group) were considered related to the study drug by the investigators, but no consistent trends in the timing of the symptoms were observed. No patient discontinued because of hypoglycaemic symptoms. The lowest glucose level measured in this study was 49 mg/dl. None of the patients had severe hypoglycaemia.

In Teneligliptin combination study with Glimepiride involving 194 patients [47], hypoglycaemic symptoms were reported by 2.1% in the Teneligliptin group and 3.1% in the placebo group during the double-blind period, showing no significant difference between the two groups. All of the events were classified as mild and did not result in study discontinuation. A reduction in the Glimepiride dose because of hypoglycaemic symptoms was not required for any patients during the study. During 40-week open label study hypoglycaemia occurred in nine patients (9.4%) in the T/T group and 12 patients (12.6%) in the P/T group during the open-label period. All episodes of hypoglycaemia were classified as mild in severity. One patient in the P/T group discontinued because of hypoglycaemia. Hypoglycaemic symptoms did not increase in elderly patients, or in patients with mild renal function impairment. In Teneligliptin-Pioglitazone combination study involving 204 patients [48], the incidence of peripheral edema at 12 weeks in the present study was consistent with that in patients receiving Pioglitazone monotherapy. In addition, there was no tendency towards an increase in the incidence of peripheral edema, even if the drug was administered for a long time and the concomitant administration of Teneligliptin and Pioglitazone did not result in an increase in the incidence of edema. During 12 week double-blind phase, hypoglycemia occurred in 2% of Teneligliptin group and in 1% & 1.9% in P/T group & T/T group respectively. Adverse events with frequency ≥5% included nasopharyngitis, upper respiratory tract inflammation, edema, gastritis, eczema, back pain, blood urine and proteinuria. In Teneligliptin combination study with Metformin [49] involving 204 patients, hypoglycemia was recorded in 2.9% patients receiving Teneligliptin which was similar to placebo.

Post marketing data collated by the innovators suggest that approximately 250,000 patients administered Teneligliptin (August 2013-July 2014) [55]. Additional adverse reactions have been identified during post-approval use of Teneligliptin therapy like hepatic dysfunction-associated cases (3 cases) & interstitial pneumonia (4 cases) during the same period. All events were non-fatal cases [55]. Similarly though rare, these adverse events for which a causality to the drug could not be ruled out are also observed with other gliptins of the class. In view of above, it is advisable to monitor patients for hepatic dysfunction with elevations of AST (glutamate oxaloacetate transaminase, GOT), ALT (glutamate pyruvate transaminase, GPT), etc. If any abnormalities are observed, it is advisable to take appropriate measures such as discontinuation of the administration. Interstitial pneumonia may occur after administration with Teneligliptin. If cough, dyspnoea, pyrexia, or abnormal chest sound (crepitations), etc. are observed, it is advisable to perform examinations including chest X-ray, chest CT scan, and serum marker test. If interstitial pneumonia is suspected, administration of the drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

Until now a number of clinical trials have been conducted evaluating the safety and efficacy of Teneligliptin in patients with type 2 diabetes mellitus. Of the 18 clinical trials conducted, 2090 patients were administered Teneligliptin and none exhibited any cardiovascular event, demonstrating its cardiac safety (based on the meta-analysis of the clinical trials on Teneligliptin) [11]-[14] [25] [33] [34] [46]-[54]. In QT/ QTc studies, a supra-therapeutic dose of Teneligliptin (160 mg/day) produced slight prolongation of the QTc interval which was detected temporally at the high concentrations of the drug (around tmax level). Teneligliptin at the daily dose of up to 40 mg (maximum dose used in clinical practice) is unlikely to cause clinically significant QTc interval prolongation [10].

7. Dosage & Administration

Oral Teneligliptin is approved as an add-on for treatment of adults with type 2 diabetes mellitus patients who have not responded adequately to treatment with diet and exercise or addition of other anti-diabetic agents such as biguanides, sulfonylureas, thiazolidinediones, glinides, α-glucosidase inhibitors or insulin. The recommended dosage of Teneligliptin is 20 mg once daily. Teneligliptin may be administered irrespective of food, preferably before breakfast. It is advisable to uptitrate the dosage to 40 mg once daily in patients who do not achieve adequate glycemic control as required.

No dosage adjustment is required in patients with mild/moderate/severe renal impairment & mild/moderate hepatic impairment. No dosage adjustment is required in elderly patients. Efficacy & safety of Teneligliptin is not studied in children. Teneligliptin should be used with caution in patients with severe hepatic impairment & those with heart failure (NYHA Class III - IV), because of a lack of clinical experience in these populations. Acute pancreatitis is observed with class of gliptins. Casual association between incretin-based drugs and pancreatitis are inconsistent with current data [56], yet, it is advisable that Teneligliptin should not be used in patients with history of pancreatitis. If the patient is already on sulfonylurea & addition of gliptin is considered, in such cases the dose of sulfonylurea should be halved & then up-titrated as required to reduce the risk of hypoglycaemia. There may be chances of hypoglycemia on co-administration of Teneligliptin with insulin & hence dosage reduction may be required. Achieving glycemic control, including meeting HbA1c goal is indicative of efficacy. It is advisable to check HbA1c; twice yearly in patients who are meeting treatment goals; every 3 months in patients whose therapy has changed &/or who are not meeting glycemic goals, more frequently as clinically warranted. Self-monitoring is advisable as needed to assist in meeting goals of therapy.

8. Place in Therapy

Diabetes is a progressive disorder. Management includes initiation with lifestyle modification *i.e.* diet & exercise but eventually will require inclusion of anti-diabetic drugs. Metformin & Sulfonylureas (SU) remain mainstay therapy in management of type 2 diabetes. These therapies gained popularity over last few decades due to ability of these drugs to deal with original pathogenic triumvirate theory of type 2 diabetes (beta-cell failure, increased hepatic glucose output and insulin resistance). In clinical scenario, Metformin therapy has been associated with gastrointestinal adverse effects [57] [58]. SU on the other hand although effective in lowering plasma glucose, work in glucose-independent manner and have been associated with variable severities of hypoglycemia, weight gain and beta-cell death [57] [59]. The United Kingdom Prospective Diabetes Study (UKPDS) was the first to show that the combination of SU and metformin resulted in a progressive decline in [beta]-cell function and by 3 years up to 50% of diabetic patients can require an additional pharmacological agent to maintain the glycosylated hemoglobin (HbA1c) <7.0% [57] [60]. Declining beta-cell function is the epitome phenomenon of worsening hyperglycemia over time [57] [61] [62]. SU's have been shown to expedite beta-cell failure and induce apoptosis at rates greater by two- to fourfold [63] [64]. It has been shown that maintaining glycemic control is difficult with SU over a period of time and up to 80% patients while on SU's will need insulin therapy, due to beta-cell exhaustion [57]. Thiazolidinedione (TZD) therapy was shown to conserve beta-cell function; however, their use has been associated with weight gain, edema and heart failure [65]. In contrast to earlier notion of tight glycemic control, the approach of management today has shifted not only towards glycemic control but also β-cell preservation so as to delay the progression of type 2 diabetes. In addition to earlier triumvirate theory, failure of incretin system has been implicated in progression of beta-cell failure. Incretin-based therapies augment the incretin system enhancing the insulin release in glucose-dependent manner and have been shown to promote beta-cell preservation [57] [60] [61] [66] [67].

The efficacy of DPP-4 inhibitors is well-established as a class without adversely affecting the survival of beta-cells. These agents offer convenient once daily dosing, are weight neutral & associated with a low risk of hypoglycaemia. Based on recommendation of various guidelines, we postulate, use of Teneligliptin could be beneficial as an add-on second-line drug in type 2 diabetes patients already on one of following anti-diabetic drugs-metformin, sulphonylurea, thiazolidinediones, α-glucosidase inhibitors, glinide and insulin.

Owing to its pharmacodynamic, pharmacokinetic & pleiotropic benefits, Teneligliptin could be of benefit early in the treatment of type 2 diabetes, in patients with diabetic nephropathy, diabetic patients with cardiovascular disease, elderly diabetic patients & patients in whom metformin therapy is intolerable or contraindicated.

9. Conclusions

Teneligliptin, a third generation gliptin offers unique pharmacodynamic advantage with unique "J-shaped anchor-lock domain" which provides potent & long duration of action. As an *α*/*β* modulator, it has insulinotropic & glucagonostatic effects controlling blood glucose for 24 hours. It may be beneficial in delaying progression of type 2 diabetes by the virtue of its *β*-cell salvager properties. Clinical studies have found improvement in beta-cell function as depicted by increase in HOMA-*β*, IGI, SUIT index & decrease in insulin resistance as depicted by decrease HOMA-R parameter. Fluctuations in blood glucose levels have been shown to cause oxidative stress and induce inflammatory markers leading to endothelial dysfunction and arteriosclerosis. Teneligliptin is found to be effective in tackling short-term glucose fluctuation as depicted by parameters like MAGE, GA & 1,5-AG.

Teneligliptin offers unique pharmacokinetic advantage with long half-life of 26.9 hours allowing convenient once daily administration irrespective of food. It has unique dual mode of elimination via renal & hepatic, and hence can be administered safely in patients with renal impairment. It does not require dosage adjustment in mild to moderate hepatic impairment. It is metabolized by cytochrome P 450 (CYP450) & flavin monooxygenases (FMO) 1 & 3 and has minimal drug-drug interaction. Owing to its effects on vascular function, Teneligliptin may show benefits with improvement in endothelial function, left ventricular function, lipid levels in addition to being weight neutral & having least chances of hypoglycemia. Current review of all clinical trials on Teneligliptin reports no major cardiac concerns observed with Teneligliptin treatment.

The suitable approach towards management of diabetes should include not only glycemic control but also early preservation of islet function, a strategy currently correct to delay progression of a disease which cannot be halted. Teneligliptin serves as an appropriate add-on to Metformin early in therapy to delay exhaustion of pancreatic islet function.

References

[1] Cho, N.H., Whiting, D., Forouhi, N., Guariguata, L., Hambleton, I., Li, R., Majeed, A., Mbanya, J.C., Montoya, P.A., Motala, A., Narayan, V., Ramachandran, A., Rathmann, W., Roglic, G., Shaw, J., Silink, M. and Zhang, P. (2015) IDF Diabetes Atlas. 7th Edition, International Diabetes Federation, Karakas Print, Brussels, 1-144.

[2] Kalra, S., Das, A.K. and Sahay, R. (2013) Managing Diabetes: The Drivers of Change. *Journal of Social Health & Diabetes*, **1**, 3-5. http://dx.doi.org/10.4103/2321-0656.109827

[3] Kalra, S. (2013) Recent Advances in Pathophysiology of Diabetes: Beyond the Dirty Dozen. *Journal of Pakistan Medical Association*, **2**, 277-280.

[4] Baetta, R. and Corsini, A. (2011) Pharmacology of Dipeptidyl Peptidase-4 Inhibitors. *Drugs*, **71**, 1441-1467. http://dx.doi.org/10.2165/11591400-000000000-00000

[5] Drucker, D.J. and Nauck, M.A. (2006) The Incretin System: Glucagon Like Peptide-1 Receptor Agonists & Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes. *The Lancet*, **368**, 1696-1705. http://dx.doi.org/10.1016/S0140-6736(06)69705-5

[6] Verspohl, E.J. (2009) Novel Therapeutics for Type 2 Diabetes: Incretin Hormone Mimetics (Glucagon-Like Peptide-1 Receptor Agonists) and Dipeptidyl Peptidase-4 Inhibitors. *Pharmacology & Therapeutics*, **124**, 113-138. http://dx.doi.org/10.1016/j.pharmthera.2009.06.002

[7] Nabeno, M., Akahoshi, F., Kishida, H., Miyaguchi, I., Tanaka, Y., Ishii, S. and Kadowaki, T. (2013) A Comparative Study of the Binding Modes of Recently Launched Dipeptidyl Peptidase IV Inhibitors in the Active Site. *Biochemical and Biophysical Research Communications*, **434**,191-196. http://dx.doi.org/10.1016/j.bbrc.2013.03.010

[8] Kushwaha, R.N., Haq, W. and Katti, S.B. (2014) Discovery of 17 Gliptins in 17-Years of Research for the Treatment

of Type 2 Diabetes: A Synthetic Overview. *Chemistry & Biology Interface*, **4**, 137-162.

[9] Röhrborn, D., Wronkowitz, N. and Eckel, J. (2015) DPP4 in Diabetes. *Frontiers in Immunology*, **6**, 1-20. http://dx.doi.org/10.3389/fimmu.2015.00386

[10] Kishimoto, M. (2013) Teneligliptin: A DPP-4 Inhibitor for the Treatment of Type 2 Diabetes. *Diabetes*, *Metabolic Syndrome and Obesity*: *Targets and Therapy*, **6**, 187-195. http://dx.doi.org/10.2147/DMSO.S35682

[11] Kadowaki, T. and Kondo, K. (2013) Efficacy, Safety and Dose-Response Relationship of Teneligliptin, a Dipeptidyl Peptidase-4 Inhibitor, in Japanese Patients with Type 2 Diabetes Mellitus. *Diabetes*, *Obesity and Metabolism*, **15**, 810-818. http://dx.doi.org/10.1111/dom.12092

[12] Eto, T., Inoue, S. and Kadowaki, T. (2012) Effects of Once-Daily Teneligliptin on 24-h Blood Glucose Control and Safety in Japanese Patients with Type 2 Diabetes Mellitus: A 4-Week, Randomized, Double-Blind, Placebo-Controlled Trial. *Diabetes*, *Obesity and Metabolism*, **14**, 1040-1046. http://dx.doi.org/10.1111/j.1463-1326.2012.01662.x

[13] Ito, R., Fukui, T., Hayashi, T., Osamura, A., Ohara, M., Hara, N., Higuchi, A., Yamamoto, T. and Hirano, T. (2015) Teneligliptin, a Dipeptidyl Peptidase-4 Inhibitor, Improves Early-Phase Insulin Secretion in Drug-Naive Patients with Type 2 Diabetes. *Drugs in R & D*, **15**, 245-251.

[14] Kutoha, E., Hiratea, M. and Ikenoa, Y. (2014) Teneligliptin as an Initial Therapy for Newly Diagnosed, Drug Naive Subjects With Type 2 Diabetes. *Journal of Clinical Medicine Research*, **6**, 287-294.

[15] Suh, S. and Kim, J.H. (2015) Glycemic Variability: How Do We Measure It and Why Is It Important? *Diabetes & Metabolism Journal*, **39**, 273-282. http://dx.doi.org/10.4093/dmj.2015.39.4.273

[16] Marling, C.R., Shubrook, H.J., Vernier, S.J., Wiley, M.T. and Schwartz, F.L. (2011) Characterizing Blood Glucose Variability Using New Metrics with Continuous Glucose Monitoring Data. *Journal of Diabetes Science and Technology*, **5**, 871-878. http://dx.doi.org/10.1177/193229681100500408

[17] Furusyo, N. and Hayashi, J. (2013) Glycated Albumin and Diabetes Mellitus. *Biochimica et Biophysica Acta*, **1830**, 5509-5514. http://dx.doi.org/10.1016/j.bbagen.2013.05.010

[18] Roche, M., Rondeau, P., Singh, N.R., Tarnus, E. and Bourdon, E. (2008) The Antioxidant Properties of Serum Albumin. *Federation of European Biochemical Societies* (*FEBS*) *Letters*, **582**, 1783-1787. http://dx.doi.org/10.1016/j.febslet.2008.04.057

[19] Dąbrowska, A.M., Tarach, J.S. and Kurowska, M. (2012) 1,5-Anhydroglucitol (1,5-AG) and Its Usefulness in Clinical Practice. *Medical and Biological Sciences*, **26**, 11-17. http://dx.doi.org/10.2478/v10251-012-0049-z

[20] Watanabe, M., Kokubo, Y., Higashiyama, A., *et al.* (2011) Serum 1,5-Anhydrodglucitol Levels Predict First-Ever Cardiovascular Disease: An 11-Year Population-Based Cohort Study in Japan, the Suita Study. *Atherosclerosis*, **216**, 477-483. http://dx.doi.org/10.1016/j.atherosclerosis.2011.02.033

[21] Ceriello, A., Quagliaro, L., Piconi, L., Assaloni, R., Da Ros, R., Maier, A., Esposito, K. and Giugliano, D. (2004) Effect of Postprandial Hypertriglyceridemia and Hyperglycemia on Circulating Adhesion Molecules and Oxidative Stress Generation and the Possible Role of Simvastatin Treatment. *Diabetes*, **53**, 701-710. http://dx.doi.org/10.2337/diabetes.53.3.701

[22] Kawano, H., Motoyama, T., Hirashima, O., Hirai, N., Miyao, Y., Sakamoto, T., Kugiyama, K., Ogawa, H. and Yasue, H. (1999) Hyperglycemia Rapidly Suppresses Flow-Mediated Endothelium-Dependent Vasodilation of Brachial Artery. *Journal of the American College of Cardiology*, **34**, 146-154. http://dx.doi.org/10.1016/S0735-1097(99)00168-0

[23] Monnier, L., Mas, E., Ginet, C., Michel, F., Villon, L., Cristol, J.P. and Colette, C. (2006) Activation of Oxidative Stress by Acute Glucose Fluctuations Compared with Sustained Chronic Hyperglycemia in Patients with Type 2 Diabetes. *The Journal of American Medical Association*, **295**, 1681-1687. http://dx.doi.org/10.1001/jama.295.14.1681

[24] Goda, M. and Kadowaki, T. (2013) Teneligliptin for the Treatment of Type 2 Diabetes. *Drugs of Today*, **49**, 615-629.

[25] Tanaka, S., Suzuki, K., Aoki, C., Niitani, M., Kato, K., Tomotsune, T. and Aso, Y. (2014) Add-On Treatment with Teneligliptin Ameliorates Glucose Fluctuations and Improves Glycemic Control Index in Japanese Patients with Type 2 Diabetes on Insulin Therapy. *Diabetes Technology & Therapeutics*, **16**, 840-845. http://dx.doi.org/10.1089/dia.2014.0095

[26] Nakamaru, Y., Hayashi, Y., Ikegawa, R., Kinoshita, S., Madera, B.P., Gunput, D., *et al.* (2014) Metabolism and Disposition of the Dipeptidyl Peptidase IV Inhibitor Teneligliptin in Humans. *Xenobiotica*, **44**, 242-253. http://dx.doi.org/10.3109/00498254.2013.816891

[27] Investi Farma S.A. (2015) Teneglucon (Teneligliptin) via Oral: Argentina Prescribing Information. http://investi.e-tradeconsult.com/teneglucon/art_234/es/

[28] Nakamaru, Y., Hayashi, Y., Sekine, M., Kinoshita, S., Thompson, J., Kawaguchi, A., *et al.* (2014) Effect of Ketoconazole on the Pharmacokinetics of the Dipeptidyl Peptidase-4 Inhibitor Teneligliptin: An Open-Label Study in Healthy White Subjects in Germany. *Clinical Therapeutics*, **36**, 760-769. http://dx.doi.org/10.1016/j.clinthera.2014.03.002

[29] Nakamaru, Y., Hayashi, Y., Davies, M., Heuer, H.J., Hisanaga, N. and Akimoto, K. (2015) Investigation of Potential Pharmacokinetic Interactions between Teneligliptin and Metformin in Steady-State Conditions in Healthy Adults. *Clinical Therapeutics*, **37**, 2007-2018. http://dx.doi.org/10.1016/j.clinthera.2015.06.012

[30] Kinoshita, S. and Kondo, K. (2015) Evaluation of Pharmacokinetic and Pharmacodynamic Interactions of Canagliflozin and Teneligliptin in Japanese Healthy Male Volunteers. *Expert Opinion on Drug Metabolism & Toxicology*, **11**, 7-14.

[31] Ceriello, A. (2000) The Post-Prandial State and Cardiovascular Disease: Relevance to Diabetes Mellitus. *Diabetes/Metabolism Research and Reviews*, **16**, 125-132. http://dx.doi.org/10.1002/(SICI)1520-7560(200003/04)16:2<125::AID-DMRR90>3.0.CO;2-4

[32] Morishita, R. and Nakagami, H. (2015) Teneligliptin: Expectations for Its Pleiotropic Action. *Expert Opinion on Pharmacotherapy*, **16**, 417-426.

[33] Hashikata, T., Yamaoka-Tojo, M., Kakizaki, R., Nemoto, T., Fujiyoshi, K., Namba, S., Kitasato, L., Hashimoto, T., Kameda, R., Maekawa, E., Shimohama, T., Tojo, T. and Ako, J. (2015) Teneligliptin Improves Left Ventricular Diastolic Function and Endothelial Function in Patients with Diabetes. *Heart Vessels*, 1-8. http://dx.doi.org/10.1007/s00380-015-0724-7

[34] Kusunoki, M., Sato, D., Nakamura, T., Oshida, Y., Tsutsui, H., Natsume, Y., Tsutsumi, K. and Miyata, T. (2015) DPP-4 Inhibitor Teneligliptin Improves Insulin Resistance and Serum Lipid Profile in Japanese Patients with Type 2 Diabetes. *Drug Research*, **65**, 532-534.

[35] Von Websky, K., Reichetzeder, C. and Hocher, B. (2014) Physiology and Pathophysiology of Incretins in the Kidney. *Current Opinion in Nephrology and Hypertension*, **23**, 54-60. http://dx.doi.org/10.1097/01.mnh.0000437542.77175.a0

[36] Girardi, A.C., Degray, B.C., Nagy, T., Biemesderfer, D. and Aronson, P. (2001) Association of Na^+-H^+ Exchanger Isoform NHE3 and Dipeptidyl Peptidase IV in the Renal Proximal Tubule. *The Journal of Biological Chemistry*, **276**, 46671-46677. http://dx.doi.org/10.1074/jbc.M106897200

[37] Girardi, A.C., Knauf, F., Demuth, H.U. and Aronson, P.S. (2004) Role of Dipeptidyl Peptidase IV in Regulating Activity of Na^+/H^+ Exchanger Isoform NHE3 in Proximal Tubule Cells. *The American Journal of Physiology—Cell Physiology*, **287**, C1238-C1245. http://dx.doi.org/10.1152/ajpcell.00186.2004

[38] Mason, R.P., Jacob, R.F., Kubant, R., Walter, M.F., Bellamine, A., Jacoby, A., Mizuno, Y. and Malinski, T. (2011) Effect of Enhanced Glycemic Control with Saxagliptin on Endothelial Nitric Oxide Release and CD40 Levels in Obese Rats. *Journal of Atherosclerosis and Thrombosis*, **18**, 774-783. http://dx.doi.org/10.5551/jat.7666

[39] Ishii, M., Shibata, R., Kondo, K., Kambara, T., Shimizu, Y., Tanigawa, T., Bando, Y.K., Nishimura, M., Ouchi, N. and Murohara, T. (2014) Vildagliptin Stimulates Endothelial Cell Network Formation and Ischemia-Induced Revascularization via an Endothelial Nitric Oxide Synthase-Dependent Mechanism. *The Journal of Biological Chemistry*, **289**, 27235-27245. http://dx.doi.org/10.1074/jbc.M114.557835

[40] Shih, C.M., Chen, Y.H., Lin, Y.W., Tsao, N.W., Wu, S.C., Kao, Y.T., Chiang, K.H., Li, C.Y., Chang, N.C., Lin, C.Y., Huang, C.Y. and Lin, F.Y. (2014) MK-0626, a Dipeptidyl Peptidase-4 Inhibitor, Improves Neovascularization by Increasing both the Number of Circulating Endothelial Progenitor Cells and Endothelial Nitric Oxide Synthetase Expression. *Current Medicinal Chemistry*, **21**, 2012-2022. http://dx.doi.org/10.2174/09298673113206660273

[41] Brandt, I., Lambeir, A.M., Ketelslegers, J.M., Vanderheyden, M., Scharpé, S. and De Meester, I. (2006) Dipeptidyl-Peptidase IV Converts Intact B-Type Natriuretic Peptide into Its Des-SerPro Form. *Clinical Chemistry*, **52**, 82-87. http://dx.doi.org/10.1373/clinchem.2005.057638

[42] Moroi, M. and Kubota, T. (2015) Diuretic and Natriuretic Effects of Dipeptidyl Peptidase-4 Inhibitor Teneligliptin: The Contribution of Glucagon-Like Peptide-1. *Journal of Cardiovascular Pharmacology*, **66**, 159-164. http://dx.doi.org/10.1097/FJC.0000000000000258

[43] Goldstein, B.J., Feinglos, M.N., Lunceford, J.K., Johnson, J. and Williams-Herman, D.E., Sitagliptin 036 Study Group (2007) Effect of Initial Combination Therapy with Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor, and Metformin on Glycemic Control in Patients with Type 2 Diabetes. *Diabetes Care*, **30**, 1979-1987. http://dx.doi.org/10.2337/dc07-0627

[44] Scheen, A.J. (2012) A Review of Gliptins in 2011. *Expert Opinion on Pharmacotherapy*, **13**, 81-99. http://dx.doi.org/10.1517/14656566.2012.642866

[45] Barnett, A., Allsworth, J., Jameson, K. and Mann, R. (2007) A Review of the Effects of Antihyperglycaemic Agents on Body Weight: The Potential of Incretin Targeted Therapies. *Current Medical Research and Opinion*, **23**, 1493-1507. http://dx.doi.org/10.1185/030079907X199691

[46] Hong, S., Park, C.Y., Han, K.A., Chung, C.H., Ku, B.J., Jang, H.C., Ahn, C.W., Lee, M.K., Moon, M.K., Son, H.S., Lee, C.B., Cho, Y.W. and Park, S.W. (2016) Efficacy and Safety of Teneligliptin, a Novel Dipeptidyl Peptidase-4 Inhibitor, in Korean Patients with Type 2 Diabetes Mellitus: A 24-Week Multicenter, Randomized, Double-Blind, Pla-

cebo-Controlled Phase III Trial. *Diabetes*, *Obesity and Metabolism*. (Epub ahead of print) http://dx.doi.org/10.1111/dom.12631

[47] Kadowaki, T. and Kondo, K. (2014) Efficacy and Safety of Teneligliptin Added to Glimepiride in Japanese Patients with Type 2 Diabetes Mellitus: A Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label, Long-Term Extension. *Diabetes*, *Obesity and Metabolism*, **16**, 418-425. http://dx.doi.org/10.1111/dom.12235

[48] Kadowaki, T. and Kondo, K. (2013) Efficacy and Safety of Teneligliptin in Combination with Pioglitazone in Japanese Patients with Type 2 Diabetes Mellitus. *Journal of Diabetes Investigation*, **4**, 576-584. http://dx.doi.org/10.1111/jdi.12092

[49] Kim, M.K., Rhee, E.J., Han, K.A., Woo, A.C., Lee, M.K., Ku, B.J., Chung, C.H., Kim, K.A., Lee, H.W., Park, I.B., Park, J.Y., Chul Jang, H.C., Park, K.S., Jang, W.I. and Cha, B.Y. (2015) Efficacy and Safety of Teneligliptin, a Dipeptidyl Peptidase-4 Inhibitor, Combined with Metformin in Korean Patients with Type 2 Diabetes Mellitus: A 16-Week, Randomized, Double-Blind, Placebo-Controlled Phase III Trial. *Diabetes*, *Obesity and Metabolism*, **17**, 309-312. http://dx.doi.org/10.1111/dom.12424

[50] Tsuchimochi, W., Uen, H., Yamashita, E., Tsubouchi, C., Sakoda, H., Nakamura, S. and Nakazato, M. (2015) Teneligliptin Improves Glycemic Control with the Reduction of Postprandial Insulin Requirement in Japanese Diabetic Patients. *Endocrine Journal*, **62**, 13-20. http://dx.doi.org/10.1507/endocrj.EJ14-0393

[51] Otsuki, H., Kosaka, T., Nakamura, K., Shimomura, F., Kuwahara, Y. and Tsukamoto, T. (2014) Safety and Efficacy of Teneligliptin: A Novel DPP-4 Inhibitor for Hemodialysis Patients with Type 2 Diabetes. *International Urology and Nephrology*, **46**, 427-432. http://dx.doi.org/10.1007/s11255-013-0552-6

[52] Kadowaki, T., Marubayashi, F., Yokota, S., Katoh, M. and Iijima, H. (2015) Safety and Efficacy of Teneligliptin in Japanese Patients with Type 2 Diabetes Mellitus: A Pooled Analysis of Two Phase III Clinical Studies. *Expert Opinion on Pharmacotherapy*, **16**, 971-981. http://dx.doi.org/10.1517/14656566.2015.1032249

[53] Kamiko, K., Aoki, K., Kamiyama, H., Taguri, M., Shibata, E., Ashiya, Y., Minagawa, F., Shinoda, K., Nakajima, S. and Terauchi, Y. (2015) Comparison of the Administration of Teneligliptin Every Day versus Every Other Day in Japanese Patients with Type 2 Diabetes: A Randomized Non-Inferior Test. *The Journal of Clinical Pharmacology*, **55**, 144-151. http://dx.doi.org/10.1002/jcph.385

[54] Wada, N., Mori, K., Nakagawa, C., Sawa, J., Kumeda, Y., Shoji, T., Emoto, M. and Inaba, M. (2015) Improved Glycemic Control with Teneligliptin in Patients with Type 2 Diabetes Mellitus on Hemodialysis: Evaluation by Continuous Glucose Monitoring. *Journal of Diabetes and Its Complications*, **29**, 1310-1313. http://dx.doi.org/10.1016/j.jdiacomp.2015.07.002

[55] Ministry of Health, Labour and Welfare & Pharmaceutical and Food Safety Bureau, Japan, Pharmaceuticals and Medical Devices Agency (PDMA) (2014) Pharmaceuticals and Medical Devices Safety Information. *Teneligliptin Hydrobromide Hydrate*, **318**, 32-37.

[56] Egan, A.G., Blind, E., Dunder, K., de Graeff, P.A., Hummer, B.T., Bourcier, T. and Rosebraugh, C. (2014) Pancreatic Safety of Incretin-Based Drugs—FDA and EMA Assessment. *The New England Journal of Medicine*, **370**, 794-797. http://dx.doi.org/10.1056/NEJMp1314078

[57] Defronzo, R.A. (2009) From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes*, **58**, 773-795. http://dx.doi.org/10.2337/db09-9028

[58] DeFronzo, R.A. and Goodman, A.M. (1995) Efficacy of Metformin in Patients with Non-Insulin-Dependent Diabetes Mellitus. The Multicenter Metformin Study Group. *The New England Journal of Medicine*, **333**, 541-549. http://dx.doi.org/10.1056/NEJM199508313330902

[59] United Kingdom Prospective Diabetes Study Group (1998) UKPDS 28: A Randomized Trial of Efficacy of Early Addition of Metformin in Sulfonylurea-Treated Type 2 Diabetes. *Diabetes Care*, **21**, 87-92. http://dx.doi.org/10.2337/diacare.21.1.87

[60] Nathan, D.M., Buse, J.B., Davidson, M.B., Heine, R.J., Holman, R.R., Sherwin, R. and Zinman, B. (2006) Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*, **29**, 1963-1972. http://dx.doi.org/10.2337/dc06-9912

[61] Bell, D.S. (2004) A Comparison of Agents Used to Manage Type 2 Diabetes Mellitus: Need for Reappraisal of Traditional Approaches. *Treatments in Endocrinology*, **3**, 67-76. http://dx.doi.org/10.2165/00024677-200403020-00001

[62] UK Prospective Diabetes Study Group (1995) U.K. Prospective Diabetes Study 16. Overview of 6 Years' Therapy of Type II Diabetes: A Progressive Disease. *Diabetes*, **44**, 1249-1258. http://dx.doi.org/10.2337/diab.44.11.1249

[63] Sawada, F., Inoguchi, T., Tsubouchi, H., Sasaki, S., Fujii, M., Maeda, Y., Morinaga, H., Nomura, M., Kobayashi, K. and Takayanagi, R. (2008) Differential Effect of Sulfonylureas on Production of Reactive Oxygen Species and Apoptosis in Cultured Pancreatic Beta-Cell Line, MIN6. *Metabolism*, **57**, 1038-1045.

http://dx.doi.org/10.1016/j.metabol.2008.01.038

[64] Maedler, K., Carr, R.D., Bosco, D., Zuellig, R.A., Berney, T. and Donath, M.Y. (2005) Sulfonylurea Induced Beta-Cell Apoptosis in Cultured Human Islets. *The Journal of Clinical Endocrinology & Metabolism*, **90**, 501-506. http://dx.doi.org/10.1210/jc.2004-0699

[65] Dormandy, J.A., Charbonnel, B., Eckland, D.J., Erdmann, E., Massi-Benedetti, M., Moules, I.K., Skene, A.M., Tan, M.H., Lefèbvre, P.J., Murray, G.D., Standl, E., Wilcox, R.G., Wilhelmsen, L., Betteridge, J., Birkeland, K., Golay, A., Heine, R.J., Korányi, L., Laakso, M., Mokán, M., Norkus, A., Pirags, V., Podar, T., Scheen, A., Scherbaum, W., Schernthaner, G., Schmitz, O., Skrha, J., Smith, U. and Taton, J., PROactive Investigators (2005) Secondary Prevention of Macrovascular Events in Patients with Type 2 Diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): A Randomised Controlled Trial. *The Lancet*, **366**, 1279-1289. http://dx.doi.org/10.1016/S0140-6736(05)67528-9

[66] Weir, G.C. and Bonner-Weir, S. (2004) Five Stages of Evolving [Beta]-Cell Dysfunction during Progression to Diabetes. *Diabetes*, **53**, S16-S21. http://dx.doi.org/10.2337/diabetes.53.suppl_3.s16

[67] Turner, R.C., Cull, C.A., Frighi, V. and Holman, R.R. (1999) Glycemic Control with Diet, Sulfonylurea, Metformin, or Insulin in Patients with Type 2 Diabetes Mellitus: Progressive Requirement for Multiple Therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *Journal of American Medical Association*, **281**, 2005-2012. http://dx.doi.org/10.1001/jama.281.21.2005